REMARKS

Reconsideration of the application is respectfully requested. Claims 20-44 are pending and at issue.

Obviousness-Type Double Patenting

Claims 20-44 have been provisionally rejected for obviousness-type double patenting over claims 36-46 of U.S. Patent Application No. 10/468,685, claims 20-34 of U.S. Patent Application No. 10/644,587, and claims 20 and 22-37 of U.S. Patent Application No. 10/644,588, in view of Applicant's allegedly admitted prior art. Applicant respectfully requests that these provisional rejections be held in abeyance because none of the patent applications containing the conflicting claims have been allowed or issued as patents.

Obviousness Rejection

Claims 20-44 have been rejected as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of the present specification. The Examiner cites Boegesoe as disclosing a method of treating depression using escitalopram, but admits that Boegesoe does not disclose the non-responsive patient population called for in the pending claims. Additionally, the Examiner cites the present specification as disclosing that clinical depression studies show that non-response or resistance to selective serotonin reuptake inhibitors (SSRIs) is substantial. According to the Examiner, it would have been obvious to administer escitalopram to treat depression in a patient who failed to respond to a non-escitalopram SSRI, such as citalopram, with a reasonable expectation of success because all SSRIs have the same mechanism of action.

Applicants respectfully disagree.

The presently claimed invention is a method of treating depression in certain treatment-resistant patients, in particular those who have not responded to treatment with an SSRI other than escitalopram. The surprising efficacy of escitalopram in such treatment-resistant patients is shown by the clinical study reported by Zimbroff discussed in the October 1, 2008 Amendment. *See*

Zimbroff, *Int. J. Neuropsychopharm.* 7(S1):S348, P02.164 (June 2004). Zimbroff found that the remission rates for patients treated with escitalopram after unsuccessful treatment with sertraline, fluoxetine, citalopram, or paroxetine were 56%, 38%, 37%, and 34%, respectively. *See* Zimbroff poster (left column, under the heading "Abstract" and subheading "Results"); *see also* Zimbroff abstract (reporting remission rates of 65% (sertraline), 44% (fluoxetine), 42% (citalopram), and 42% (paroxetine)).

Upon failure to respond to an SSRI (other than escitalopram), a patient would not reasonably be expected to respond to escitalopram as it, too, is an SSRI - i.e., escitalopram works by the same mechanism of action as other SSRIs. The Examiner cites to this common functionality as supporting a conclusion of obviousness. *See* Office Action, p. 7. However, quite the opposite must be concluded. If a depressed patient does not improve when treated with a drug that inhibits the reuptake of serotonin, one of ordinary skill in the art would reasonably conclude that alternative treatment options (i.e., treatments that do not rely on inhibiting the reuptake of serotonin to provide an antidepressant effect) should be employed. For instance, a more appropriate treatment might be found with non-SSRIs such as bupropion (Wellbutrin®), tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs). Put another way, if patients are non-responsive to an initial SSRI, it would be logical to conclude that serotonin reuptake inhibition alone is not an effective treatment for that patient. Yet, escitalopram surprisingly has been shown to have this advantageous effect.

This result is particularly surprising for patients who were not successfully treated with citalopram, which is a racemate that contains both R-citalopram and escitalopram. The Examiner states several times that it would have been obvious to administer escitalopram to a patient who has failed to respond to citalopram. *See* Office Action, pp. 6-7. However, since it was known that "almost the entire 5-HT [serotonin] uptake inhibition [resides] in the (+)-citalopram enantiomer" (Boegesoe, col. 2, lines 38-40), one of ordinary skill would not expect escitalopram to have different efficacy. That is, if a patient did not respond to the active ingredient (escitalopram) when administered in the form of its racemate (citalopram), that patient would not be expected to respond

to the same active ingredient when administered in a purified form (escitalopram). At best, one of ordinary skill would expect escitalopram to provide increased potency - i.e., achieving the same response in the patient, but requiring only half the dose to do so. As stated in the present specification, the inventors surprisingly discovered that the R-enantiomer in citalopram has a *negative* effect on escitalopram resulting in citalopram's inferior efficacy (*see* specification, p. 2, lines 13-14). This is demonstrated by the Zimbroff study, where escitalopram was found to be therapeutically effective while citalopram (at significantly higher doses, in some cases 3 times higher) was not.

None of the cited references discloses or suggests the detrimental influence of the R-enantiomer, or that administration of escitalopram alone would provide the demonstrated superior therapeutic effect over racemic citalopram. This is particularly relevant to the non-obviousness of claims 41-44, which specify that the initial SSRI treatment is citalopram.

Lastly, the Examiner states that the Zimbroff clinical study was not considered because the abstract was published after the effective filing date of the instant application. *See* Office Action, p. 8. Zimbroff shows that escitalopram was effective in patients who failed to respond to therapeutic treatment with citalopram and other SSRIs (such as fluoxetine, paroxetine, and sertraline). It is well established that later-published facts can be relevant to a non-obviousness argument. *See Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1150 (Fed. Cir. 1983) ("Facts determinable at a later time may serve to evidence nonobviousness as of the time the invention was made."). Therefore, this reference may be properly relied upon to show unexpected results even though it does not constitute prior art. Accordingly, Zimbroff should be considered in any obviousness determination.

For at least the foregoing reasons, claims 20-44 are not obvious, and applicants respectfully request that this rejection be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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